# A I D S TREATMENT N E W S

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## Contents


**Treatment Interruption; Advanced HIV; New Ideas: Dr. Cal Cohen Interview on Retroviruses Conference (part 2 of 2)..... 2**

The conclusion of Dr. Cohen's interview includes an in-depth look at current thinking on treatment interruption, strategies for highly treatment-experienced patients, and other topics from the recent Retroviruses conference.

**SARS Web Information..... 6**

Where to find current information about Severe Acute Respiratory Syndrome (SARS), a new disease that can cause severe or fatal pneumonia.

**Abacavir Arm Stopped in Clinical Trial..... 6**

A government clinical trial stopped treatment with abacavir plus AZT plus 3TC, due to more viral rebound than other treatments in the study. Many unknowns remain.

**Huge Medicaid Cuts Weighed in Washington..... 7**

A $92 billion Medicaid cut passed by the U.S. House of Representatives, and a plan by the Bush Administration to reduce entitlement funding of medical care for the poor and elderly and give states more power to choose whose benefits are ended, could seriously reduce HIV care in the coming decade.

**Africa Activism: Money for AIDS Not for War; South Africa Antiretrovirals..... 8**

Africa Action seeks organizational endorsements for prioritizing an epidemic that has already killed 25 million people. Separately, South Africa's Treatment Action Campaign seeks international support for government cooperation in making

# AIDS Treatment News

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*AIDS Treatment News* reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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# Treatment Interruption; Advanced HIV; New Ideas: Dr. Cal Cohen Interview on Retroviruses Conference (part 2 of 2)

by John S. James

In our last issue Cal Cohen, M.D., discussed starting antiretroviral treatment, new information on protease inhibitors, and antiretroviral toxicity. Here he looks at treatment interruption, and treatment of patients with advanced illness who have already received many antiretrovirals. We also asked about an early experiment with a human monoclonal antibody, which might lead to a different kind of treatment given by injection every two or three weeks.

The interview took place on February 21.

## Treatment Interruptions

**Dr. Cohen:** There were a couple of very important presentations on treatment interruptions [see abstracts #64 through #68lb on this topic]. I would summarize them as follows:

We continue to learn from studies that in some cases people can safely stop their medications. If somebody has had a good CD4 rise and then stops medication, CD4 counts do not plummet rapidly, on average. The viral load, even as it goes up, may leave most people able

to tolerate some time off antiretrovirals if that is their choice. The risks include a few percent who can have symptoms associated with HIV rebound -- similar to what some have when first exposed to HIV. We have also learned at past meetings that the other risk of stopping -- rapidly falling CD4 counts -- is greatest in those who have a history of very low counts -- suggesting that immune reconstitution is not always complete for those who have ever had very low CD4 counts. But even this is a generalization -- there are some with low counts in the past who have stopped and had some time off with stable counts -- they just need more frequent monitoring if they do stop.

New data at this meeting highlighted a caution -- that a few percent of people will develop viral resistance when stopping antiretrovirals. Understanding of why and when that happens is still evolving. But it appears that if your viral load is higher than 50 and you stop your antiretrovirals, that is when you are more likely to develop resistance. And this resistance is most likely to drugs with a “low genetic barrier” to the development of resistance - especially 3TC and the non-nukes [efavirenz and nevirapine].

We are seeing results of studies showing that people can take weeks or even months off antiretrovirals (long-cycle approaches to treatment interruption). For example, a Thai trial compared short treatment cycles (7 days on and 7 days off), vs. continuous treatment, vs. a strategy of stopping when the CD4 counts are above 350 and starting only after a 30% drop in the counts.[1] The researchers noted that their volunteers needed to be on medications only 33% of the time with this CD4-guided strategy. This approach is promising to reduce drug exposure. And it is similar to the strategy being tested in the international "SMART" trial -- the largest trial ever attempted in our field. (SMART compares long-cycle interruptions to continuous therapy. It is tackling a key issue in structured treatment interruption, which is whether it makes a difference in the long term. Readers can learn more about the SMART study at http://www.smart-trial.org.)

But an important caution about treatment interruption also came from this trial,[1] which showed that the 7-day-on-7-day-off antiretroviral regimen for people with well-suppressed virus did not always work. This trial had 73 volunteers, of whom about a third did 7 days on and 7 days off, and there were virologic escapes. There may be reasons that explain it, including underlying resistance, or these volunteers not always having less than 50 when they stopped. These are just conjectures, as the research team did not fully explain why their results differed so much from other studies that showed successful suppression even after 7 days off. The bottom line is that the 7-7 regimen is still a research approach with rules yet to be understood, which is why we remind people that this is still research and not a recommendation. If everybody looked at the 7-7 data from Dr. Dybul at the National Institutes of Health and started doing it, the Thai data suggests that as many as half of the people trying it could have virologic escape. Researchers and doctors are cautious because sometimes we learn later on that problems occur. We need time and experience to understand the newer strategies in order to know how to apply our findings.

So these days if someone is considering a treatment interruption, and they want to be as conservative as possible -- meaning to conserve the drugs they are on now for use next time -- some of the studies suggested treatment interruption may be safe, but it is also important to do so in a way that minimizes creating resistance. Resistance occurs while the drugs are leaving the bloodstream and are present in concentrations too low to stop the virus from growing. So we can take advantage of the higher genetic barrier to resistance of boosted protease inhibitors. One approach I use is a week of boosted dual protease inhibitors to avoid resistance. If someone is on, say, AZT plus 3TC plus efavirenz, I may substitute a dual boosted protease inhibitor combination, Kaletra plus saquinavir, for example, for a week. This allows the AZT, 3TC, and efavirenz to leave the bloodstream while continuing viral suppression. Then you can stop the protease inhibitors, and these drugs have a high enough genetic barrier that you are quite unlikely to lose them to resistance. Otherwise, you might lose 3TC or efavirenz -- and it seems to me a good use of that week on an alternative regimen to not risk losing those very precious drugs. Get them out of your system while the virus is suppressed.

**James:** As a practical matter, do you have trouble with reimbursement if you prescribe these drugs for just one week?

**Dr. Cohen:** In my experience, no, because it appears the same as if I am just switching to this combination; no insurance refuses to pay for medication switches. And certainly our pharmacies here in Massachusetts are enlightened enough that if I want to give somebody a week's supply instead of a month's supply they are OK with that. It may be different elsewhere.

## Choosing Drugs for Highly Treatment Experienced Patients ("Deep Salvage")

**James:** What was new at this meeting for people who have had extensive antiretroviral treatment, and have already developed resistance to a number of the drugs?

**Dr. Cohen:** At this meeting we saw two very important pieces of the puzzle. One area is new drugs. Another is an idea on how to wait instead of switching antiretrovirals too soon.

Given that there are important new drugs coming, the question is what to do if somebody is on a combination now that is holding them at some acceptable viral load. If they do not have enough new drugs that can work for them to create an effective, potent regimen that makes it likely they will re-establish suppression, we have seen that if you switch too early they will lose those drugs and be back where they started, only worse since they now have even fewer options. So there has always been an interest in postponing the switch until you have a good switch. The difficult question for a couple of years has been, what do you do while you wait? Because keeping someone on a regimen allowing partial suppression, but unfortunately also allowing the virus to create more and more mutations, creates more and more cross resistance, potentially losing options you've been trying to save somebody for.

No one has a great answer, but Steve Deeks presented some very preliminary but creative work, that for many was one of the highlights of the meeting for innovativeness.[2] Since after resistance non-nukes are generally useless, he has people on a combination of nucleoside analogs and protease inhibitors, as most of us do. He then focused on a group who were still receiving benefit from the antivirals -- those whose current viral load on meds was lower than their set

point -- suggesting that at least some of the meds were working. Then he thought, maybe we could "save" a class -- and keep people on just nucleoside analogs, or just protease inhibitors, minimizing creating more resistance to either one class or the other -- and minimizing toxicity from one class as well.

He showed that when he stopped the protease inhibitors, maintaining the nucleosides only, at least for weeks if not months, the viral load stayed suppressed; he could maintain this viral load even without the protease inhibitors for months. Five patients did the reverse, and stayed on the protease inhibitors, and he did see a viral load increase of a little over half a log -- suggesting that, at least for now, stopping the protease inhibitors and maintaining nucleosides may be a better way to postpone switching and preserve the protease inhibitors for the future. If you are off the protease inhibitors you will not develop new PI mutations, so drugs like tipranavir may stay more active for you. That's the logic.

Dr. Deeks also pointed out that this approach does not last forever. It may be a stalling maneuver. It does provide food for thought, and maybe another option for a while. But he noted that in time the nucleoside-inhibitor-only approach will lead to rebound -- so it might be necessary to restart the protease inhibitors for some period of time, to take advantage of the fact that the protease inhibitors can reduce the blood level of even resistant virus. The key is to emphasize that these observations are the beginning of a story -- and we have much to learn about when these observations hold true, as well as when we will see different outcomes. But it has some relevance for some people now.

There are new drugs coming. We saw data on tipranavir that shows that the company now has a dose worth using, and that it works well against many protease-inhibitor-resistant mutations. T-20 is already well established and approved for sale at least in the U.S. as of March 2003; in this meeting we saw data to show that T-1249 works if you have T-20 resistance, and it works quite well. We also saw data about other new classes of drugs, including many other entry inhibitors, CCR-5 inhibitors, and one drug from a completely new class that may be a viral assembly inhibitor. Many of these new drugs are still only in the test tube; there is a little clinical data. But it was promising that people are finding new drugs and new drug classes that work against resistant viruses.

## Human Monoclonal Antibody

**James:** What do you think about the early test of the anti-HIV antibody TNX-355 -- a new kind of possible treatment that was injected once, and still inhibited HIV two weeks later?[3]

**Dr. Cohen:** It's not clear ultimately where this drug will go -- but there might be an injectable treatment given every two weeks or so. In the trial so far they gave only one dose, and two weeks later the virus reached its lowest point. We have never before seen a drug that a single dose took two weeks to reach its maximum response; it is not entirely clear why that happened. This finding was curious but suggests that this drug binds to the cells for a prolonged period and maintains the effects for far longer than our usual oral medication. It raises a host of questions because we have not used drugs with these characteristics before.

**James:** Activists were disappointed that there was no human data on TMC125, a new and very powerful non-nucleoside.[4]

**Dr. Cohen:** Yes, there may be issues with the formulation. This drug has been burdened by a formulation that requires many pills per day, and the company is working hard to improve on that before moving ahead. As I understand it, they are closer to proceeding to the next phase of research.

There are many drugs we will hear about over time -- some will be developed more slowly than others. We are hearing less data about some potential drugs since many trials are just under way. Because we do not hear about something does not necessarily mean there is no new information about it. Sometimes the trials are being planned or have started, but are not mature enough to be presented at scientific meetings.

## Summary

**James:** Could you summarize some of your main take-home points from the meeting?

**Dr. Cohen:**

(1) We continue to learn that we are far from preventing HIV infection with a vaccine. Therefore prevention through behavior changes that are maintained is critical to protecting oneself reducing the size of the epidemic. We also don't know much more about the risk from re-exposure to HIV, so for now we suggest caution as more is learned.

(2) We know that treatment works, and we are learning more about the tradeoffs with different approaches. There is no perfect regimen for everyone, but clearly some choices have well-established advantages over others.

(3) We must continue to be vigilant about side effects. While searching for ways to both prevent and reverse them, we must also be alert for newer side effects that we do not yet know much about. We are only six years into the "HAART" era -- and without a cure in place, we have decades to go.

(4) Starting treatment is no longer a single decision to be made once -- people can stop and restart multiple times in different patterns. The benefits and risks of these approaches are finally beginning to be defined. And through longer-term studies finally underway, we hope to be able to move from the era of knowing that we can stop medications in some cases, to knowing whether we should stop medications. It will take many people in long-term studies to answer this question.

(5) The only way forward is more research. We all need to be vigilant about supporting HIV research, as well as advocating for our own field.

## References

Note: These references are to the 10th Conference on Retroviruses and Opportunistic Infections, Boston February 10-14, 2003. They are available at http://www.retroconference.org and will remain there for about a year. The abstracts should be readable on all computers, but the browser's Internet security setting should not be too high, or the software to search the abstracts will not work.

1. J Ananworanich, P Cardiello, P Srasuebkul, and others. HIV-NAT 001.4: A Prospective Randomized Trial of Structured Treatment Interruption in Patients with Chronic HIV Infection. [Abstract #64]

2. SG Deeks, JN Martin, R Hoh, T Wrin, C Petropoulos, and RM Grant. Continued reverse

transcriptase inhibitor therapy is sufficient to maintain short-term partial suppression of multi-drug resistant viremia. [Abstract #640]

3. DR Kuritzkes, JM Jacobson, W Powderly and others. Safety and preliminary anti-HIV activity of an anti-CD4 mAb (TNX-355; formerly HU5A8) in HIV-infected patients. [Abstract #13]

4. K Das, AD Clark, and PL Boyer. Could multiple modes of binding of a potent NNRTI TMC125-R165335 explain its potency against common drug-resistant mutants? [Abstract #613 - Poster available]

# SARS Web Information

by John S. James

Almost everyone has now heard of SARS (severe acute respiratory syndrome), a new disease that can cause a serious and sometimes fatal pneumonia. As we go to press (April 2, 2003) the news is changing very rapidly. Just a week ago it looked like SARS might be dying out -- but then Hong Kong reported over 50 new cases in one day. Conferences and other public events are being postponed or cancelled in that city and some other parts of Asia. This disease could end on its own, or it could become a worldwide pandemic and kill many people. Currently there are over 80 suspected cases in the U.S., most acquired from travel abroad.

SARS is believed to be caused by a previously unknown virus. Some but not all patients have severe breathing difficulties and need a respirator. So far the fatality rate has been about 4%. Recently Hong Kong physicians reported success in treating seriously ill patients with antibodies from those who had recovered -- a well-known technique that has been used successfully with other infectious diseases.

At this time experts believe that SARS is spread mostly by close personal contact, as in hospitals or homes, especially by coughing or sneezing. Some patients appear to be much more contagious than others. No one knows how well the infection can travel through the air in public places. It might also be spread by objects recently handled by an infected person.

## For Current Information

One place to start is a Web page by the U.S. National Library of Medicine:
http://www.nlm.nih.gov/medlineplus/severeacuterespiratorysyndrome.html

For more detailed information, see the U.S. Centers for Disease Control and Prevention (CDC) page: http://www.cdc.gov/ncidod/sars/

We have not yet seen any HIV-specific information about SARS.

## Comment

We suggest that more be done to support people in complying with public-health directives -- especially travelers far from home who are asked not to fly if they have possible symptoms. If they fear being stranded in a foreign country thousands of miles from home with no place to stay, uncertain medical care, and problems getting a flight home when they recover, they will have strong incentive to lie and conceal their illness. It would cost little for public-health systems to help make arrangements for the few travelers affected at this time.

New diseases will become increasingly serious due to crowded populations, massive air travel, and possibly bioterrorism. Proper support for public health, long neglected by governments that care only for the rich (who can afford private medicine), will become a life-or-death issue for everyone.

# Abacavir Arm Stopped

# in Clinical Trial

by John S. James

A major government clinical trial comparing three HIV treatments stopped the arm using abacavir plus AZT plus 3TC (Trizivir®) alone, after patients in that arm "experienced virologic failure earlier and more frequently than patients who were randomized to receive either of the other two treatment regimens being evaluated in the study." However, all three of the study arms seemed to do well virologically, given the relatively advanced HIV infection the volunteers started with. And "there were no concerns about the toxicity of the study drugs."

This trial (known as AACTG protocol A5095) compared abacavir plus AZT plus 3TC vs. efavirenz (Sustiva®) plus AZT plus 3TC, vs. all four drugs (abacavir plus efavirenz plus AZT plus 3TC). In this study the volunteers were antiretroviral naive, but started with a high viral load (median over 78,000 copies, with 43% of the volunteers having over 100,000) and low CD4 count (median 238). A data review at 32 weeks found that 21% of those randomly assigned to the Trizivir alone still had a viral load over 200 copies after at least 16 weeks of treatment (which was defined as "virologic failure" in this study), compared to 10% of the volunteers in the other two groups combined. The difference was seen both in the group with viral load over 100,000 copies when they started the trial, and the group with lower viral load. Because the difference was statistically significant and met the pre-determined standard for stopping a treatment arm, the Data Safety Monitoring Board (DSMB) had no choice but to stop abacavir plus AZT plus 3TC and offer the participants other treatment. A March 10, 2003, letter from the U.S. Division of AIDS to the researchers, containing all the information initially available, is at: http://www.niaid.nih.gov/daids/default.htm.

Because the other two arms of this trial are continuing, the DSMB released the least amount of information necessary, to avoid any risk of biasing study results. For example, we do not know if the virologic "failure" usually meant a viral load barely above 200, or considerably higher. Also, we have no information about adherence and missing doses. The study was double-blinded and placebo controlled, so all volunteers took five pills at night and two in the morning, and if some were more careless about missing the morning than the evening dose, that could have biased the result in the direction seen, since all the efavirenz was in the evening dose, but every drug in the Trizivir-only arm would have been affected by missing the medicine in the morning.

Some additional information will be submitted to the International AIDS Society conference, July 13-17 in Paris; however, the other two study arms will still be ongoing, so full information may not be available even then. Continuing the two remaining arms will help address the question of whether adding a fourth drug to certain 3-drug HAART combination regimens provides enough additional virologic benefit to be worth the added cost in side effects and expense.

### Comment

There is no perfect HIV treatment, and we have not seen any rush to change drug regimens because this Trizivir arm was stopped. The new information does have doctors' attention, and will be reflected in medical consensus as more is learned.

# Huge Medicaid Cuts Weighed in Washington